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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/597,517	06/20/2000	Thangavel Kuberasampath	JJJ-P07-503	5819

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EXAMINER	
KEMMERER, ELIZABETH	

ART UNIT	PAPER NUMBER
1646	25

DATE MAILED: 11/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/597,517	KUBERASAMPATH ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,23 and 49-76* is/are pending in the application.

4a) Of the above claim(s) *71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,23,49-70 and 72-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *3,23 and 49-76* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). 20 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Request for RCE

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02 September 2003 has been entered.

37 C.F.R. § 1.126

New claims numbered 76-81 were submitted. Since claims numbered 71-75 were not entered in the after final amendment of 04 November 2002 (Paper No. 16), they are not pending, and the next available claim number was 71. Therefore, newly submitted claims numbered 78-81 have been renumbered as 71-76 by the examiner as authorized by 37 CFR 1.126.

Election/Restriction

Newly submitted claim 71 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The invention being examined is directed to therapeutic methods, classified in Class 514, Subclass 1, for example. Newly presented claim 71 is directed to a method for identifying agents that stimulate *in vivo* expression of a morphogen, classified in Class 435, Subclass 4, for example. Those in the art recognize that this subject matter is divergent, given the natures of the method steps involved. For

example, the therapy method claims require a step of administering to a patient population. Although claim 71's screening steps are now recited in the examined therapeutic method claims, examination of claim 71 presents an undue search burden to the Office, since the search for the examined invention is limited to therapy. Claim 71 would significantly broaden that search by requiring a search for screening methods for agents that are not necessarily useful in therapy.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, separate search requirements, and art-recognized divergent subject mater, restriction for examination purposes as indicated is proper.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 71 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Status of Application, Amendments And/Or Claims

The amendment filed 02 September 2003 (Paper No. 22) has been entered in full. Claims 1, 2, 4-22 and 24-48 are canceled. Claim 71 is withdrawn from consideration as discussed above. Claims 3, 23, 49-70 and 72-76 are under examination to the extent they read on the elected invention.

Claim Objections

Claims 72 and 74-76 are objected to because of the following informalities: the claims depend in part from a non-elected claim. Appropriate correction is required.

35 U.S.C. § 112, First Paragraph

(1) Claims 3, 23, 49-70 and 72-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth at pp. 2-3 of Paper No. 10 (28 January 2002) and pp. 2-6 of the previous Office Action (Paper No. 15, 30 July 2002).

Applicant's arguments (pp. 9-10, Paper No. 22, 02 September 2003) have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant argues that the claims have been amended to obviate the rejection, since a screening step for identifying the agents has been added. This is not found to be persuasive, because the skilled artisan cannot envision the detailed chemical structure of the recited agents, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more

than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

(2) Claims 3, 23, 49-70 and 72-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth at pp. 3-4 of Paper No. 10 (28 January 2002) and pp. 2-6 of the previous Office Action (Paper No. 15, 30 July 2002).

Applicant's arguments (pp. 10-15, Paper No. 22, 02 September 2003) have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant argues that the previous office action's concern regarding Example 15 is misplaced. Specifically, Applicant asserts that he disclosed cell culture system for identifying the agents need not correlate to model systems for the diseases recited in the claims, because any agent that can stimulate morphogen production *in vitro* in a tissue culture system can reasonably be expected to stimulate morphogen production *in vivo*. Applicant reasons that, because morphogens can be found in several body fluids, it can reasonably be concluded that an agent that stimulates morphogen production locally will lead to

a systemic elevation of morphogen level *in vivo*. Applicant concludes that the ability of an agent to stimulate morphogen production *in vitro* in a given cell (for example, a lung cell) can be reasonably correlated with the agent's ability to stimulate morphogen production *in vivo*, at least in the same cell type, and that the secreted morphogen will be systemically delivered to other tissues via body fluids. This has been fully considered but is not found to be persuasive. Example 15 is a prophetic example. Essentially, it is a suggestion as to how to screen for agents that would affect the level of a morphogen. The experimental protocols suggested are extremely broad and vague. Very little experimental procedure details are provided. Furthermore, the example does not set forth any agents that were successfully identified this way. The example does not expressly state that it is desirable to isolate agents that stimulate *in vivo* expression of an endogenous morphogen which could then be administered in an undefined therapeutically effective amount to a mammal suffering from tissue destructive effects associated with an inflammatory response to an injured tissue or ischemia-reperfusion injury or hyperoxia injury, as required by the claims. Applicant has provided little or no guidance beyond the mere suggestion of a general screening assay to enable one of ordinary skill in the art to determine, without undue experimentation, agents that would have the therapeutically effective activity required by the claims. Although the specification outlines art-recognized procedures for screening for agents that alter endogenous morphogen concentrations, this is not adequate guidance as to the nature of

active agents that may be screened, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

Applicant argues that tests for "therapeutically effective amounts" are not required for enablement. Citing *Ex parte Skuballa*, 12 USPQ2d 1570 (BPAI 1989), Applicant argues that "an effective amount" is definite in light of the supporting disclosure which provides guidelines as to the intended utilities and how the uses can be effected. Applicant urges that the instant specification meets these criteria. Applicant argues that "therapeutically effective amount" depends upon a number of factors, such as those listed at pp. 56-57 of the specification, and can be determined without undue experimentation by one skilled in the art, such as a physician. This has been fully considered but is not found to be persuasive. *Ex parte Skuballa*, *supra*, is not applicable to the instant fact pattern since the issue in *Ex parte Skuballa* was a rejection under 35 U.S.C. § 112, second paragraph. The instant rejection is made under 35 U.S.C. § 112, **first** paragraph, involving a question of enablement, not definiteness. Furthermore, the enablement issue regarding "therapeutically effective amount" involves whether it is actually possible to achieve a stimulation of *in vivo* expression of an endogenous morphogen to a therapeutically effective amount indirectly, that is, by the administration of an "agent" identified by a screening procedure as required by the claims. At the time of the invention, it was known that morphogens could be administered directly to achieve a therapeutic effect, and the amounts needed for the effect were known. See, for example, U.S> Patent 5,011,691 to Oppermann et al., of record). However, it was not known in

the prior art, nor is it disclosed in the instant specification, how to administer an agent that would stimulate endogenous morphogen production to an extent that the morphogens are elevated to a therapeutically effective amount, as required by the claims. The structure, dosages, administration methods, etc. of the agents are not disclosed in the specification and were not known in the prior art. Elucidation of these details involves significant experimentation, amounting to an undue amount of experimentation. Proper analysis of the Wands factors has been provided in previous office actions.

Applicant argues that the previous office action's concerns regarding Laufer, Hogan and Roberts are rendered moot by the amendments to the claims, which now set forth methods of identifying the "agents" required by the claims. Applicant urges that evidence would have to be provided to show why a skilled artisan, in light of the specification, would not be able to identify an "agent" in accordance with step (i) of the claims. Applicant reasons that if a single agent of desired effect can be identified according to step (i), no matter how inefficient or unsuccessful the actual processes are, the amended claims are enabled. The examiner disagrees. Whether or not an undue amount of experimentation would have been required of the skilled artisan to practice the claimed invention directly involves consideration of the inefficiency or lack of success of the recited processes, as they speak to the following Wands factors: the amount of experimentation required, the amount of direction or guidance provided by the specification, the complexity of the invention, the presence/absence of working examples, and the state of the art at the time of the invention. In the instant

application, a large quantity of experimentation is necessary to identify agents having the activities required by the claims, since the specification provides very little direction or guidance regarding the nature of potential agents. Also, there are no working examples directed to such agents. The nature of the invention is very complex, as it requires regulation of endogenous gene expression levels. The state of the prior art is silent with respect to agents that can cause a sufficient increase in the levels of endogenous morphogens. There is a large degree of unpredictability is any complex biological regulatory system. Finally, the breadth of the claims is very large, as they fail to recite any structural limitations for the recited agents. In fact, they are single means claims. They can also be characterized as reach-through claims, since the specification does not disclose any "agents" as described in the claims, only the method of screening for them. Clearly, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant argues that the mere absence of a working example is not in itself evidence that the claimed invention is non-enabled. The examiner agrees. However, as outlined above, this is one of the Wands factors that needs to be considered when making a determination of whether or not the amount of experimentation required is undue. There are other factors that point toward a conclusion of undue experimentation, and thus lack of enablement, for the instant claims as discussed above.

Applicant argues that the amount of experimentation is not undue, since a large number of candidate compounds can be routinely screened. Applicant

refers to *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986) and *In re Buchner*, 929 F.2d 660 (Fed. Cir. 1991) as supporting this argument. This has been fully considered but is not found to be persuasive. In both cases cited by Applicant, the claims at issue were products, not methods of using products identified by a screening process. In other words, the cases did not involve reach-through claims, as the instant case does. Whereas the instant application may enable methods of screening for agents *per se*, it does not enable methods of administering those agents for therapeutic effect, for reasons set forth above.

Applicant also argues that the screening method need not be a foolproof one. Applicant cites *Johns Hopkins University v. Cellpro., Inc.*, 152 F.2d 1342 (Fed. Cir. 1998) in support of this argument. Applicant summarizes the findings in the case, and concludes that a skilled artisan would have been able to identify agents as recited in the claims through routine screening. Again, the fact pattern is different in the instant case since the products themselves are not being claimed. Also, the *Hybritech* and *Johns Hopkins* cases involved antibodies, a class of structurally similar compounds. The instant claims merely recite "agent", which can be anything, including peptides, antibodies, organic compounds, inorganic compounds, gases, mimetics, vitamins, etc. Generating and screening a single class of compounds, antibodies, is far more straightforward than the instant claims which recite screening for any structure (agent) having a particular activity followed by administering the agent to achieve a therapeutic effect.

Applicant urges that, to rebut their argument, it would have to be shown why one of ordinary skill in the art would have been unable to make the claimed invention without undue experimentation, and that the amount of experimentation is due to insufficient disclosure of the specification rather than that the nature of the problem to be solved. This is what has been established in the rejection. A large quantity of experimentation is necessary to identify agents having the activities required by the claims, since the *specification* provides very little direction or guidance regarding the nature of potential agents. Also, the specification provides no working examples directed to such agents. The nature of the invention is very complex, as it requires regulation of endogenous gene expression levels. Contrary to Applicant's implication, the complexity of the invention is a factor to be considered when determining whether or not the amount of experimentation required Is undue. This has long been established by case law. The state of the prior art, another factor that must be considered, is silent with respect to agents that can cause a sufficient increase in the levels of endogenous morphogens. There is a large degree of unpredictability is any complex biological regulatory system. Finally, the breadth of the claims is very large, as they fail to recite any structural limitations for the recited agents. In fact, they are single means claims. They can also be characterized as reach-through claims, since the specification does not disclose any "agents" as described in the claims, only the method of screening for them. Clearly, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

(3) Claims 50-70 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection, previously set forth at pp. 6-7 o the previous Office Action (Paper No. 15, 30 July 2003).

Applicant argues (p. 15, Paper No. 22, 02 September 2003) the paragraph bridging pp. 9-10 provides explicit support for the claimed invention by referring to the inflammatory response. Applicant argues that a skilled artisan would readily recognize that the claimed invention would be suitable to treat all disease conditions associated with inflammatory responses, especially those described explicitly in claims 50-70. This has been fully considered but is not found to be persuasive. The specification as originally filed simply does not refer to any of the specific diseases listed in claims 50-70, nor do these specific diseases flow naturally from the specification.

(4) Claims 72, 73, 75 and 76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification as originally filed does not disclose the claimed methods wherein the cell is form a cell type that produces measurable level of morphogen, wherein the cell originates from the same type of tissue as the injured tissue, wherein the level of morphogen is determined by abundance of mRNA or protein, or the source of the mRNA or protein. Applicant also ahs not indicated where support for the new claim language can be found in the specification as originally filed. Applicant's attention is directed to MPEP 2163.06: "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure."

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (703) 308-2673. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne L. Eyler, Ph.D. can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ECK

ELIZABETH KEMMERER
PRIMARY EXAMINER